Clinical Presentation of Severe COVID-19 Disease in Children and Adolescents

Disease Burden – Severity of Illness of COVID-19 in Children

- Incidence and mortality:
  - Lower compared to adults: 23 vs 413/100,000
  - But rates in children are increasing
  - Low compared to adults: 23 vs 413/100,000
- Hospitalization rates in US (weekly):
  - Among hospitalized 30% required ICU care, 6-9%
  - Less likely to develop severe illness
- Multisystem in children
- Acute COVID disease

COVID-19 and Healthcare Disparities

- On average 4x higher infection rate for adults and children of racial and/or ethnic minority groups compared to non-Hispanic whites
- Disparities in disease severity have also been well documented: on average 3 out of every 4 children hospitalized with COVID-19 and/or MIS-C come from racial and/or ethnic minority groups
- These inequalities are driven by a combination of societal- and individual-level factors

How to Recognize COVID-19 in Children?

- Incubation period: average (range) of days (3-14 days)
- Signs or symptoms:
  - Non-specific
  - Difficult to differentiate from other infections or non-infectious causes
- Asymptomatic 16% - 50%
  - Symptom-based screening for identification of SARS-CoV-2 in children not useful

Clinical Spectrum of COVID-19 in Hospitalized Children

- Acute COVID disease
  - Respiratory disease
  - Other non-respiratory presentations
- Multisystem inflammatory syndrome in children (MIS-C)
  - Rare complication of COVID in children
  - Associated with shock and multiorgan failure requiring ICU care
  - UK: pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV2 (PIMS-TS)
  - Case definitions vary depending on country and region, an internationally accepted case definition is still evolving

Introduction

- Novel coronavirus noted in cluster of pneumonia cases in Wuhan (Hubei Province, China) in December 2019
- New virus identified and named SARS-CoV-2, and disease designated as COVID-19
- Rapid spread in China and worldwide
- WHO declared pandemic on March 11, 2020
- As of January 16th 2021:
  - Cumulative cases: 93.9 million+
  - Cumulative deaths: 2 million+
- Children/adolescents account for only small proportion of COVID cases
  - 2.1-12% per National Statistics (Asia, Europe, North America)

Disease Burden – Severity of Illness of COVID-19 in Children

- US Cases and Deaths by Age Group as of Jan 4

COVID-19 and Healthcare Disparities

- Rates of SARS-CoV-2 infection by race/ethnicity and socioeconomic status in DC/Maryland

How to Recognize COVID-19 in Children?

- Symptoms and clinical features of COVID-19
- Symptomatic children and young adults with symptomatic SARS-CoV-2

Clinical Spectrum of COVID-19 in Hospitalized Children

- Epidemic curve of acute-COVID-19 and MIS-C cases in the Tri-State Region
Signs and Symptoms on Admission by Clinical Syndrome

- Respiratory: fever 87% + cough 81% + dyspnea 64%
- Other: fever 67% + GI symptoms (abdominal pain, diarrhea, emesis) 52%
- MIS-C: fever 100% + GI symptoms 79% + Rash 39%


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Acute Respiratory Illness

<table>
<thead>
<tr>
<th>With presence of LRTI</th>
<th>Abnormal Radiographic findings obtained</th>
<th>Need for respiratory support among those with LRTI</th>
<th>ARDS among those with LRTI</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zachariah n=50</td>
<td>50%</td>
<td>70%</td>
<td>64%</td>
<td>84%</td>
</tr>
<tr>
<td>Kainth n=45</td>
<td>52%</td>
<td>54%</td>
<td>65%</td>
<td>84%</td>
</tr>
<tr>
<td>Fernandes n=281</td>
<td>51%</td>
<td>49%</td>
<td>58%</td>
<td>84%</td>
</tr>
<tr>
<td>Götzinger n=363</td>
<td>39%</td>
<td>47%</td>
<td>52%</td>
<td>84%</td>
</tr>
</tbody>
</table>

- Radiographic findings: variable (CT): B/L or unilateral patchy infiltrates; focal infiltrates; pleural effusions, pneumothorax
- Duration of IMV: median 5-9 days (IQR 2-27days)
- Patients with ARI compared to MIS-C cases:
  - Older: median age 14y vs 7y
  - More co-morbidities incl obesity

Zachariah P, et al. JAMA Pediatrics October 2020, Volume 174, Number 10

Laboratory Findings of COVID-19

- Variable
- Lymphopenia (neutropenia) 44% - 72%
- ALC did not differ significantly in patients with and without severe disease
- Potential markers of severe disease — elevated WBC and inflammatory markers (eg, CRP, procalcitonin, interleukin 6, ferritin, D-dimer) at admission or during hospitalization


What Are Risk Factors for Severe Disease?

- Most information based on observational studies
- US/Ca ICU study: 83% had co-morbidities
- Analysis of deceased 75% had co-morbidities pediatric patients

Management of COVID-19 in Children

**Hospital admission:**
- Severe or critical LRTI
- At risk for severe disease
- Infants < 30 days old with fever

**Supportive care:**
- Resp. Support
- Fluid and electrolytes
- Monitoring for cytokine release syndrome (RR, SO2, biomarkers → CRP, PCT, d-dimer, ferritin, LDH, IL-6)
- Consider thromboprophylaxis

**Therapeutics**
- Remdesivir
  - approved in US for children ≥12y and ≥40kg
  - EUA for children <12y but ≥3.5kg
- Corticosteroids (hypoxia, need for resp. support)

- Baricitinib + remdesivir: EUA for children ≥2y

- Immune modulators e.g. anakinra, tocilizumab

Multisystem Inflammatory Syndrome in Children

**Rare complication (prolonged fever, inflammation, multiorgan failure incl shock)**
- Acute COVID 322 per 100,000 vs MIS-C 2 per 100,000,
- Most reported from Europe, Canada, US, South Africa but not from China or other Asian countries
- Median age 8-11 years; mostly (>70%) previously healthy
- Black (25-45%) and hispanic (30-40%) disproportionately affected compared to Asian (3-28%) and white (15-25%)

**Pathophysiology:**
- Post-infectious complication secondary to Immune dysregulation
- Delayed occurrence, diagnostic profile: 50% ab → CRP, 34% ab → PCT, 5% ab → PCT
- Clinical similarities to Kawasaki disease (KD), macrophage activation syndrome (MAS), and cytokine release syndrome.

- The mechanisms by which SARS-CoV-2 triggers the abnormal immune response are unknown

How Do Children with MIS-C Present?

- 100% Persistent fevers (median duration four to six days)
- 60 - 100% GI symptoms (abdominal pain, vomiting, diarrhea)
- Appendicitis?, terminal ileitis, colitis
- 45 - 76% Rash
- 30 - 81% Conjunctivitis
- 27 - 76% Mucous membrane involvement
- 29 - 58% Neurocognitive symptoms (headache, lethargy, confusion)
- 21 - 65% Respiratory symptoms
- 10 - 16% Sore throat
- 8 - 17% Myalgia
- 9 - 16% Swollen hands/feet
- 6 - 16% Lymphadenopathy

Case Definitions for Multisystem Inflammatory Syndrome in Children

**Elevated inflammatory markers:**
- CRP ≥ 100 mg/L
- ESR ≥ 80 mm/h
- D-dimer ≥ 1000 μg/L
- Fibrinogen ≥ 750 mg/dL
- Ferritin ≥ 1000 ng/mL
- Procalcitonin ≥ 1000 pg/mL
- Interleukin-6 ≥ 15 ng/mL

**Elevated cardiac markers:**
- Troponin ≥ 99th percentile
- BNP or NT-pro-BNP ≥ 99th percentile

**Other abnormal markers:**
- Lymphopenia
- Neutrophilia
- Thrombocytosis
- Hypoalbuminemia

**Laboratory findings**

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Organ manifestations and Complications in MIS-C

- 32 – 76% Shock
- 22 – 64% Criteria met for complete Kawasaki dx
- 51 – 90% Myocardial dysfunction
- 5 – 21% Hepatitis or hepatomegaly
- 6 – 7% Encephalopathy, seizures, coma, or meningitis/encephalitis

Echocardiography
- Depressed LV function (30-40%)
- Coronary artery (CA) abnormalities, including dilation or aneurysm (8-19%)
- Mitral valve regurgitation
- Pericardial effusion

Differentiating MISC from Kawasaki Disease

1. Age: MIS-C older children and adolescents ≥ Kawasaki Disease: Infants and young children
2. Race/ethnicity: Black, Hispanic ≥ Higher incidence in East Asia, children of Asian descent
3. GI Symptoms: ++ ≥ +++
4. Myocardial dysfunction and shock: ++ ≥ +++
5. Higher CRP, ferritin, D-Dimer: + ≥ ++++
6. Lower lymphocyte, platelet counts: ≥
7. Risk of CA involvement in MIS-C is comparable with the risk in classic KD

Management

1. Treatment
   - Based on presentation: Inflammatory shock vs cardiac dysfunction vs KD-like features
   - Shocks: cardiotonic, according to standard protocols (epinephrine, norepinephrine and milrinone)
   - CCMC experience: +++++
   - IVIG: 100%
   - Aspirin: 88%
   - Methylprednisolone: 42%
   - Echocardiography: 42%
   - In case of incomplete response: IVIG 2nd dose: 10%
   - Aleverap: 12%
   - Tocilizumab: 9%
   - Infliximab: 3%

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   - IVIG 2nd dose: 10%
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   In case of complete response:
   - IVIG: 100%
   - Aspirin: 88%
   - Methylprednisolone: 70%
   - Echocardiography: 42%

   Outcome:
   - CCMC experience: +++++
   - 0 deaths
   - Cardiac function at discharge: Always normal: 42%
   - Depressed then normalized: 18%
   - Mildly depressed: 27%

   Systemic review: n=855 patients
   - 11 deaths
   - 20% mildly depressed cardiac function
   - Prognosis unclear at this time
   - Long term follow up studies lacking for now

Summary

- Risk for COVID-related morbidity and mortality and need for hospital care is significantly less in children compared to adults
- One third of children requiring hospital care (comparable to adults) require intensive care because they may develop respiratory failure, myocarditis, shock, acute renal failure, coagulopathy, and multi-organ system failure
- Multisystem Inflammatory Syndrome in Children (MIS-C) is a rare but significant complication, that is still incompletely understood in terms of its pathogenesis and prognosis
- Children with co-morbidities and obesity maybe at an increased risk for severe disease manifestations, more studies needed to describe diagnosis-specific risk profile, and possible clinical interventions and strategies to reduce hospitalization risk
- Longstanding disparities in healthcare highlighted also for children, with a disproportionate negative effect on communities of color

Thank you for your attention!